DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/22/2008 has been entered.

Status of Claims

2. Claims 21, 23-26, 33-42, 44, 58-62, 66-69, 74-75, 81-82, 85-87, 90-93 and 96 are cancelled. Claims 1-20, 22, 27-32, 43, 45-57, 63-65, 70-73, 76-80, 83-84, 88-89, 94-95 and 97-98 are pending. Claims 10-15, 29, 32, 45-57, 63-65, 70-73, 76-80, 83-84, 88-89, 94-95, and 97-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/09/2006. Claims 1-9, 16-20, 22, 27-28, 30-31 and 43 are under examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-9, 16-20, 22, 27-28, 30-31 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al.[1]

In response to the rejection, Applicant argues that the Office has failed to provide any rationale for why one of ordinary skill would focus on SEQ ID NO: 888 as a starting point when Krieg et al. teaches over 1000 immunostimulatory sequences.

Applicant's argument has been considered, however, it is not found persuasive. SEQ ID NO: 888 of Krieg et al. is an immunostimulatory sequence, along with his many other sequences. Krieg et al. teaches methodically modifying immunostimulatory sequences to modulate the immunomodulatory activities of the immunostimulatory sequences. Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the immunostimulatory sequences disclosed by Krieg et al., including SEQ ID NO: 888. Moreover, neither the Office nor Krieg et al. have to specifically set forth a rationale for the use of SEQ ID NO: 888 instead of the other sequences because KSR forecloses the argument that specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR*, 82 USPQ2d at 1396.

Applicant also argues that the Office has misapplied the teachings of Krieg et al. To support Applicant's arguments, Applicant notes that exchange of adenine for a thymidine to increase the immunostimulatory activity taught by Krieg et al. is limited to SEQ ID NO: 320, wherein the adenine to thymidine exchange is located between two CpG motifs. Applicant continues with the argument by asserting that the Office has

[1] Krieg et al. WO 2001/22972, published April 05, 2001.

misconstrued this particular teaching because the cited teaching is at determining the structure-function relationship of the CpG motifs by replacing bases adjacent to the CpG motif while maintaining the two CpG motifs within the sequence. Applicant also argues that the Office used impermissible hindsight in making a prima facie case of obviousness.

Applicant's arguments have been considered, however, it is not found persuasive. Contrary to Applicant's assertion, the Office has not failed to properly understand the teachings of Krieg et al. Krieg et al. clearly establishes that the exchange of adenine to thymidine increases the immunostimulatory activities of immunostimulatory sequences. The Office directs Applicant's attention to the previously cited passages, along with lines 2-5, page 6, in particular. While it is noted that the increase in immunostimulatory activities by an exchange of adenine to thymidine discussed by Krieg et al. is discovered by modifying the bases adjacent to CpG motifs, as presented in SEQ ID NO: 320; however, this particular teaching of Krieg et al. is not intended to be limiting to solely SEQ ID NO: 320, as evidenced by the discussion provided by Krieg et al., at lines 2-5, page 26 of the Krieg et al. reference. At lines 2-5, page 26 of the disclosure of Krieg et al., Krieg et al. clearly teaches that the exchange of adenine to thymidine increases immunostimulatory activities of immunostimulatory sequences. Hence, while Applicant's arguments has been considered, it is not found persuasive for the Office has properly construed the teachings and suggestions made by Krieg et al. Krieg et al. clearly establishes that the exchange of adenine to thymidine increases immunostimulatory activities of immunostimulatory sequences.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the prima facie case of obviousness established by the Office takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure. The art, Krieg et al. clearly establishes that the exchange of adenine to thymidine increases immunostimulatory activities of immunostimulatory sequences. Hence, it would have been prima facie obvious for one of ordinary skill in the art to exchange the adenine in SEQ ID NO: 888 of Krieg et al. to thymidine. The exchange would render SEQ ID NO: 888 the same as claimed SEQ ID NO: 1. Therefore, the rejection is proper.

Applicant additionally continues with arguments by citing various case laws that Applicant asserts to firmly support that a reason must exist for one of ordinary skill in the art to choose a specific compound as a lead compound when presented with several other compounds.

Applicant's arguments have been considered, however, it is not found persuasive. KSR forecloses the argument that specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR*, 82 USPQ2d at 1396.

Applicant furthers arguments by stating that the claimed invention is based on the surprising discovery of a nucleotide sequence having activity that is the same as or greater than that of SEQ ID NO: 246 of Krieg et al. To support this position, Applicant directs the Office attention to the Examples, and conclude that in view of the extensive screening required, wherein the claimed nucleotide sequence was identified after screening over 100 different sequences for such an activity profile, Krieg et al. did not know and could not predict which sequence would have an activity profile approximating or exceeding that of SEQ ID NO: 246. Applicant concludes with the assertion that the facts strongly support the absence of a reasonable expectation of success necessary to make the prima facie case of obviousness, and/or the existence of unexpected results necessary to rebut the prima facie case even if made.

Applicant's claims of unexpected results and absence of reasonable expectation of success has been considered, however, they are not found persuasive. Applicant is reminded that the standard for obviousness is not absolute predictability. Rather the standard is reasonable expectation of success. Krieg et al. clearly demonstrated that the exchange of adenine for thymidine would increase the immunostimulatory activity of a sequence.

Regarding Applicant's assertion of unexpected results, this has been considered, however, it is not found persuasive. While it is noted that Applicant directs the Office

attention to the Examples to support Applicant's assertion of unexpected results, the Office cannot find evidence that supports unexpected results. Applicant's specification contains 3 Examples, none of which is directed at comparing Applicant's SEQ ID NO: 1 to SEQ ID NO: 246 of Krieg et al. In the instant case, nothing exists in the Examples to demonstrate unexpected results. Hence, this argument is not persuasive. Additionally, while it is noted that the Applicant's disclosure, excluding the Examples, provides that the claimed invention is directed at the unexpected discovery that SEQ ID NO: 1 is more immunostimulatory that previously reported immunostimulatory sequences; however, should Applicant relies on this disclosure for any claim of unexpected results, Applicant is reminded that the increased in immunostimulatory activities with the exchange of adenine for thymidine is clearly expected by Krieg et al. Hence, the exchange of adenine for thymidine in SEQ ID NO: 888 of Krieg et al. is expected to render the immunostimulatory activity of SEQ ID NO: 888 to be enhanced or increased. Thus, while Applicant asserts unexpected results, it is found that the results has long been expected and predicted by Krieg et al.

As previously presented, the claims are directed toward a composition comprising an immunostimulatory nucleic acid comprising/consisting of the nucleic acid sequence of SEQ ID NO:1. Claim 3, which depends on independent claim 1, requires the composition to further comprise an antigen, which is later limited to a microbial antigen by claim 4. Claim 5 further limits the microbial antigen of claim 4 to a viral antigen. Claim 6 additionally limits the antigen of claim 3 to those encoded by a nucleic acid vector. Claim 7, which is interpreted to recite a dependency to claim 6, requires

that the nucleic acid vector be different from the immunostimulatory nucleic acid. Claim 8 further limits the antigen of claim 3 to a peptide antigen. Claim 9, which depends on claim 1, requires the composition to further comprise an adjuvant. Claim 16, which depends on claim 1, requires the immunostimulatory nucleic acid to have a nucleic acid backbone that is modified. Claim 17, which depends on claim 16, requires the modification to be a phosphorothioate modification. Claim 18, which depends on claim 16, requires the modified backbone to a chimeric backbone. Claim 19, which depends on claim 16, requires the immunostimulatory nucleic acid to have all modified backbones. Claim 20, which depends on claim 1, requires the composition to comprise a pharmaceutically acceptable carrier. Claim 22, which depends on claim 1, requires the immunostimulatory nucleic acid to comprise at least four CpG motifs. Claim 27, which depends on claim 1, requires the immunostimulatory nucleic acid to be formulated as a nutritional supplement. Claim 28, which depends on claim 28, requires the supplement be formulated as a capsule, pill, or a sublingual tablet. Claim 30, which depends on claim 1, requires the immunostimulatory nucleic acid be formulated for parenteral administration. Claim 31, which depends on claim 1, requires the immunostimulatory nucleic acid be formulated in a sustained released device. Claim 43, further limits the sustained release to a microparticle.

Additionally, claim 2, which depends on claim 1, limits the immunostimulatory nucleic acid sequence to consist of SEQ ID NO: 1. SEQ ID NO: 1 has the following sequence: TCGTCGTTTCGTCGTTTTGTCGTT.

Krieg et al. teaches a composition comprising of an immunostimulatory nucleic acid, wherein the immunostimulatory nucleic acid sequence consists of the sequence: TCGTCGTTTCGTCGTTTTGACGTT, SEQ ID NO: 888. SEQ ID NO: 888 of Krieg et al. has at least 4 CpG motifs and is 24 nucleic acid resides in length. The number of CpG motifs and nucleic acid residues present in SEQ ID NO: 888 of Krieg et al. is the same as that of Applicant's claimed SEQ ID NO: 1. The difference between SEQ ID NO: 888 of Krieg et al. and Applicant's claimed SEQ ID NO: 1 is: Nucleic acid residue at position 20 of the sequences are not the same. Nucleic acid residue at position 20 of SEQ ID NO: 888 of Krieg et al. is A (adenine), and the nucleic acid residue at position 20 of Applicant's claimed SEQ ID NO: 1 is T (thymidine). However, Krieg et al. suggests the exchange of the adenine with thymidine. [Lines 19-20, page 143, in particular.] Krieg et al. notes that the exchange resulted in slightly higher immunostimulatory activity induced by the immunostimulatory nucleic acid. Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have exchanged adenine for thymidine. One of ordinary skill in the art at the time the invention was made would have been motivated to do so enhance the immunostimulatory activity of the immunostimulatory nucleic acid. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because Krieg et al have demonstrated the enhancement of immunostimulatory activity.

Krieg et al. further teaches the addition of an antigen to the composition. [Lines 19-21, page 6; Lines 3-5, page 38, in particular.] The antigen that Krieg et al. teaches

includes microbial antigens, viral antigens, antigens encoded by a nucleic acid vector, and a peptide antigen. [Claims 38-39, page 160, in particular.] The nucleic acid vector that Krieg et al. teaches is different from the immunostimulatory nucleic acid. Krieg et al. also teaches the use of adjuvants with the composition. [Lines 15-16, page 94, in particular.] Krieg et al. additionally teaches the use of nucleic acid backbones that are modified. [Claim 18, page 158, in particular.] The modified backbone that Krieg et al. teaches includes phosphorothioate backbones and chimeric backbones. [Claims 19-20, page 158, in particular] Krieg et al. also teaches modifying all the backbones. [Claim 21, page 158, in particular.]

Krieg et al. also teaches the addition of a pharmaceutically acceptable carrier with the composition. [Lines 1-3, page 3, in particular.] Krieg et al. further teaches that the composition be formulated as a nutritional supplement. [Lines 25-28, page 6, in particular] Krieg et al. teaches that the supplement be formulated as a capsule, pill, or a sublingual tablet. Krieg et al. further teaches providing the composition in a form ready for parenteral administration. [Lines 10-15, page 13, in particular.] Krieg et al. additionally teaches the sustained release, specifically microparticle, form of the composition. [Lines 12-13, page 10, in particular.]

Conclusion

5. No claims are allowed.

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the

application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Le/
Patent Examiner, Art Unit 1648

/E. L./